

TRANSMITTAL LETTER TO THE UNITED STATES  
DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C. 371

29342/36206A

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

10/031556

INTERNATIONAL APPLICATION NO.  
PCT/US00/11129INTERNATIONAL FILING DATE  
26 April 2000PRIORITY DATE CLAIMED  
30 April 1999

TITLE OF INVENTION

UNIT DOSAGE FORM

APPLICANT(S) FOR DO/EO/US

PULLMAN, William Ernest and WHITAKER, John Steven

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
  - a. ☐ is attached hereto (required only if not communicated by the International Bureau).
  - b. ☒ has been communicated by the International Bureau.
  - c. ☒ is not required, as the application was filed in the United States Receiving Office (RO/US).
- ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
  - a. ☐ is attached hereto.
  - b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
- ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
  - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
  - b. ☐ have been communicated by the International Bureau.
  - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
  - d. ☒ have not been made and will not be made.
- ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
- ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
- ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

**Items 13 to 20 below concern document(s) or information included:**

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

**Return receipt postcard**

531 Rec'd PCT

19 OCT 2001

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 1.53) **10/031356**

INTERNATIONAL APPLICATION NO. **PCT/US00/11129**

ATTORNEY'S DOCKET NUMBER **29342/36206A**

24. The following fees are submitted..

**BASIC NATIONAL FEE ( 37 CFR 1.492 (a) (1) - (5) ) :**

- ☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO ..... **\$1040.00**
- ☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO ..... **\$890.00**
- ☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... **\$740.00**
- ☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... **\$710.00**
- ☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfy provisions of PCT Article 33(1)-(4) ..... **\$100.00**

**ENTER APPROPRIATE BASIC FEE AMOUNT =**

**\$890.00**

Surcharge of **\$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).

**\$0.00**

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE
Total claims	17 - 20 =	0	x \$18.00
Independent claims	2 - 3 =	0	x \$84.00
Multiple Dependent Claims (check if applicable).			<input type="checkbox"/>

**\$0.00**  
**\$0.00**  
**\$0.00**

**TOTAL OF ABOVE CALCULATIONS =**

**\$890.00**

☐ Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.

**\$0.00**

**SUBTOTAL =**

**\$890.00**

Processing fee of **\$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).

**\$0.00**

**TOTAL NATIONAL FEE =**

**\$890.00**

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable).

☐

**\$0.00**

**TOTAL FEES ENCLOSED =**

**\$890.00**

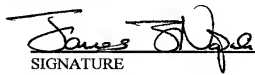
Amount to be:  
refunded \$  
charged \$

- a. ☒ A check in the amount of **\$890.00** to cover the above fees is enclosed.
- b. ☐ Please charge my Deposit Account No. \_\_\_\_\_ in the amount of \_\_\_\_\_ to cover the above fees. A duplicate copy of this sheet is enclosed.
- c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **13-2855** A duplicate copy of this sheet is enclosed.
- d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

**NOTE:** Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

**SEND ALL CORRESPONDENCE TO:**

**NAPOLI, James J.**  
Customer No. 04743  
**Marshall, Gerstein & Borun**  
6300 Sears Tower  
233 South Wacker Drive  
Chicago, Illinois 60606  
United States of America

  
SIGNATURE

**James J. Napoli**

NAME

**32,361**

REGISTRATION NUMBER

**19 October 2001**

DATE

52 REG OF 317 19 OCT 2001

IN THE UNITED STATES PATENT  
AND TRADEMARK OFFICE

  
Richard Zimmermann

Commissioner of Patents  
Washington, D.C. 20231

Please amend the above-identified application  
as follows:

Page 1, after the title, please delete the  
CROSS-REFERENCE TO RELATED APPLICATION in its entirety  
and insert therefor:

--CROSS-REFERENCE TO RELATED APPLICATIONS

This is the U.S. national phase application of International Application No. PCT/US00/11129, filed on April 26, 2000, which claims the benefit of provisional patent application Serial No. 60/132,036, filed April 30, 1999.--

IN THE CLAIMS:

Cancel claims 18 and 19 without prejudice.

Amend claims 7-9 as follows:

7. (Amended) The dosage form of claim 1, 2, 3, 4, 5, or 6 wherein the unit dose is in a form selected from the group consisting of a liquid, a tablet, a capsule, and a gelcap.

8. (Amended) The dosage form of claim 1, 2, 3, 4, 5, or 6 wherein the unit dose is in the form of a tablet.

9. (Amended) (Amended) The dosage form of claim 1, 2, 3, 4, 5, or 6 for use in treating a condition wherein inhibition of PDE5 is desirable.

## REMARKS

Claims 1-19 are pending in the application.  
Claims 18 and 19 have been cancelled. Therefore, claims  
1-17 are at issue in this application.

The amendments are described in more detail below. Pursuant to 37 C.F.R. §1.121, a marked-up version of the changes made to the claims by the present amendment is attached hereto following the signature page of this amendment. The first page of the marked-up version of the changes is captioned "Version With Markings to Show Changes Made."

This preliminary amendment adds no new matter. The specification has been amended to insert a cross-reference to a related application. Claims 7-9 have been amended to improve the form of the claims.

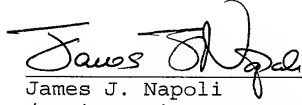
It is submitted that the amendment should be entered, and that the claims are of a proper form and scope for allowance. An early and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Respectfully submitted,

**MARSHALL, GERSTEIN & BORUN**

By

A handwritten signature in dark ink, appearing to read "James J. Napoli", written over a horizontal line.

James J. Napoli  
(Registration No. 32,361)  
Attorneys for Applicants  
6300 Sears Tower  
233 South Wacker Drive  
Chicago, Illinois 60606  
(312) 474-6300

Chicago, Illinois  
October 19, 2001

10/031556

531 Rec'd PCT.

19 OCT 2001

Version With Markings to Show Changes Made  
(U.S. National Stage of PCT/US00/11129  
filed October 19, 2001)

IN THE SPECIFICATION:

The following cross-reference to related application has been inserted into the specification:

**CROSS-REFERENCE TO RELATED APPLICATIONS**

This is the U.S. national phase application of International Application No. PCT/US00/11129, filed on April 26, 2000, which claims the benefit of provisional patent application Serial No. 60/132,036, filed April 30, 1999.

IN THE CLAIMS:

Claims 18 and 19 have been cancelled without prejudice.

Claims 7-9 have been amended as follows:

7. (Amended) The dosage form of [claims 1 through 6] claim 1, 2, 3, 4, 5, or 6 wherein the unit dose is in a form selected from the group consisting of a liquid, a tablet, a capsule, and a gelcap.

8. (Amended) The dosage form of [claims 1 through 6] claim 1, 2, 3, 4, 5, or 6 wherein the unit dose is in the form of a tablet.

9. (Amended) The dosage form of [claims 1 through 6] claim 1, 2, 3, 4, 5, or 6 for use in treating a condition wherein inhibition of PDE5 is desirable.



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## UNIT DOSAGE FORM

CROSS REFERENCE TO RELATED APPLICATIONS

- 5                    This application claims the benefit of  
provisional patent application Serial No.  
60/132,036, filed April 30, 1999.

FIELD OF THE INVENTION

10

- The present invention relates to a highly  
selective phosphodiesterase (PDE) enzyme inhibitor  
and to its use in a pharmaceutical unit dosage form.  
In particular, the present invention relates to a  
15                    potent inhibitor of cyclic guanosine 3',5'-mono-  
phosphate specific phosphodiesterase type 5 (PDE5)  
that when incorporated into a pharmaceutical product  
is useful for the treatment of sexual dysfunction.  
The unit dosage form described herein is character-  
20                    ized by selective PDE5 inhibition, and accordingly,  
provides a benefit in therapeutic areas where  
inhibition of PDE5 is desired, with minimization or  
elimination of adverse side effects resulting from  
inhibition of other phosphodiesterase enzymes.

25

BACKGROUND OF THE INVENTION

- The biochemical, physiological, and  
clinical effects of cyclic guanosine 3',5'-mono-  
30                    phosphate specific phosphodiesterase (cGMP-specific  
PDE) inhibitors suggest their utility in a variety  
of disease states in which modulation of smooth  
muscle, renal, hemostatic, inflammatory, and/or

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endocrine function is desired. Type 5 cGMP-specific phosphodiesterase (PDE5) is the major cGMP hydro-  
lyzing enzyme in vascular smooth muscle, and its  
expression in penile corpus cavernosum has been  
5 reported (Taher et al., *J. Urol.*, 149, p. 285A  
(1993)). Thus, PDE5 is an attractive target in the  
treatment of sexual dysfunction (Murray, *DN&P* 6(3),  
pp. 150-56 (1993)).

A pharmaceutical product, which provides a  
10 PDE5 inhibitor, is currently available and marketed  
under the trademark VIAGRA<sup>®</sup>. The active ingredient  
in VIAGRA<sup>®</sup> is sildenafil. The product is sold as an  
article of manufacture including 25, 50, and 100 mg  
tablets of sildenafil and a package insert. The  
15 package insert provides that sildenafil is a more  
potent inhibitor of PDE5 than other known phospho-  
diesterases (greater than 80 fold for PDE1 inhibi-  
tion, greater than 1,000 fold for PDE2, PDE3, and  
PDE4 inhibition). The IC<sub>50</sub> for sildenafil against  
20 PDE5 has been reported as 3 nM (*Drugs of the Future*,  
22(2), pp. 138-143 (1997)) and as 3.9 nM (Boolel et  
al., *Int. J. of Impotence*, 8, pp. 47-52 (1996)).  
Sildenafil is described as having a 4,000-fold  
selectivity for PDE5 versus PDE3, and only a 10-fold  
25 selectivity for PDE5 versus PDE6. Its relative lack  
of selectivity for PDE6 is theorized to be the basis  
for abnormalities related to color vision.

While sildenafil has obtained significant  
commercial success, it has fallen short due to its  
30 significant adverse side effects, including facial  
flushing (10% incidence rate). Adverse side effects  
limit the use of sildenafil in patients suffering  
from vision abnormalities, hypertension, and, most

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significantly, by individuals who use organic nitrates (Welds et al., *Amer. J. of Cardiology*, 83(5A), pp. 21(C)-28(C) (1999)).

5       The use of sildenafil in patients taking organic nitrates causes a clinically significant drop in blood pressure which could place the patient in danger. Accordingly, the package label for sildenafil provides strict contraindications against its use in combination with organic nitrates (e.g.,  
10       nitroglycerin, isosorbide mononitrate, isosorbide nitrate, erythrityl tetranitrate) and other nitric oxide donors in any form, either regularly or intermittently, because sildenafil potentiates the hypotensive effects of nitrates. See C.R. Conti et al., *Amer. J. of Cardiology*, 83(5A), pp. 29C-34C  
15       (1999). Thus, even with the availability of sildenafil, there remains a need to identify improved pharmaceutical products that are useful in treating sexual dysfunction.

20       Daugan U.S. Patent 5,859,006 discloses certain tetracyclic derivatives that are potent inhibitors of cGMP-specific PDE, or PDE5. The IC<sub>50</sub> of the compounds disclosed in U.S. Patent No. 5,859,006 is reported in the range of 1 nM to 10 µM.  
25       The oral dosage for such compounds is 0.58 mg daily for an average adult patient (70 kg). Thus, unit dosage forms (tablets or capsules) are reported as 0.2 to 400 mg of active compound. Significant adverse side effects attributed to compounds  
30       disclosed in U.S. Patent No. 5,859,006 are not disclosed.

Applicants have discovered that one such tetracyclic derivative, (6R,12aR)-2,3,6,7,12,12a-

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hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-  
pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione,  
alternatively named (6R-trans)-6-(1,3-benzodioxol-5-  
yl)-2,3,6,7,12,12a-hexahydro-2-methylpyrazino-  
5 [1',2':1,6]pyrido[3,4-b]indole-1,4-dione, and re-  
ferred to herein as Compound (I), can be admin-  
istered in a unit dose that provides an effective  
treatment without the side effects associated with  
the presently marketed PDE5 inhibitor, sildenafil.  
10 Prior to the present invention such side effects  
were considered inherent to the inhibition of PDE5.

Significantly, applicants' clinical  
studies also reveal that an effective product having  
a reduced tendency to cause flushing in susceptible  
15 individuals can be provided. Most unexpectedly, the  
product also can be administered with clinically  
insignificant side effects associated with the com-  
bined effects of a PDE5 inhibitor and an organic  
nitrate. Thus, the contraindication once believed  
20 necessary for a product containing a PDE5 inhibitor  
is unnecessary when Compound (I) is administered as  
a unit dose of about 1 to about 20 mg, as disclosed  
herein. Thus, the present invention provides an  
effective therapy for sexual dysfunction in indi-  
25 viduals who previously were untreatable or suffered  
from unacceptable side effects, including individ-  
uals having cardiovascular disease, such as in  
individuals requiring nitrate therapy, having  
suffered a myocardial infarction more than three  
30 months before the onset of sexual dysfunction  
therapy, and suffering from class 1 congestive heart  
failure, or individuals suffering from vision ab-  
normalities.

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The present invention provides Compound (I) in a unit dosage form. That is, the present invention provides a pharmaceutical unit dosage form suitable for oral administration comprising about 1 to about 20 mg Compound (I).

#### SUMMARY OF THE INVENTION

The present invention provides a pharmaceutical dosage form for human pharmaceutical use, comprising about 1 to about 20 mg of (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione in a unit dosage form suitable for oral administration.

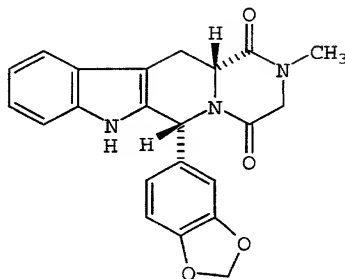
The present invention further provides a method of treating conditions where inhibition of PDE5 is desired, which comprises administering to a patient in need thereof an oral dosage form containing about 1 to about 20 mg of a selective PDE5 inhibitor, as needed, up to a total dose of 20 mg per day. The invention further provides the use of an oral dosage form comprising a selective PDE5 inhibitor at a dosage of about 1 to about 20 mg for the treatment of sexual dysfunction.

Specific conditions that can be treated by the present invention, include, but are not limited to, male erectile dysfunction and female sexual dysfunction, particularly female arousal disorder, also known as female sexual arousal disorder.

In particular, the present invention is directed to a pharmaceutical unit dosage composition

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comprising about 1 to about 20 mg of a compound having the structural formula:



said unit dosage form suitable for oral administration, and method of treating sexual dysfunction using the pharmaceutical unit dose composition.

#### DETAILED DESCRIPTION

For purposes of the present invention as disclosed and described herein, the following terms and abbreviations are defined as follows.

The term "container" means any receptacle and closure therefor suitable for storing, shipping, dispensing, and/or handling a pharmaceutical product.

The term " $IC_{50}$ " is the measure of potency of a compound to inhibit a particular PDE enzyme (e.g., PDE1c, PDE5, or PDE6). The  $IC_{50}$  is the concentration of a compound that results in 50% enzyme inhibition in a single dose-response experiment. Determining the  $IC_{50}$  value for a compound is readily

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carried out by a known *in vitro* methodology generally described in Y. Cheng et al., *Biochem. Pharmacol.*, 22, pp. 3099-3108 (1973).

5 The term "package insert" means information accompanying the product that provides a description of how to administer the product, along with the safety and efficacy data required to allow the physician, pharmacist, and patient to make an informed decision regarding use of the product. The  
10 package insert generally is regarded as the "label" for a pharmaceutical product.

The term "oral dosage form" is used in a general sense to reference pharmaceutical products administered orally. Oral dosage forms are recognized by those skilled in the art to include such  
15 forms as liquid formulations, tablets, capsules, and gelcaps.

The term "vision abnormalities" means abnormal vision characterized by blue-green vision  
20 believed to be caused by PDE6 inhibition.

The term "flushing" means an episodic redness of the face and neck attributed to vasodilation caused by ingestion of a drug, usually accompanied by a feeling of warmth over the face and  
25 neck and sometimes accompanied by perspiration.

The term "free drug" means solid particles of drug not intimately embedded in a polymeric coprecipitate.

The presently claimed dosage form  
30 preferably is packaged as an article of manufacture for human pharmaceutical use, comprising a package insert, a container, and a dosage form comprising about 1 to about 20 mg of Compound (I)

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The package insert provides a description of how to administer a pharmaceutical product, along with the safety and efficacy data required to allow the physician, pharmacist, and patient to make an informed decision regarding the use of the product. The package insert generally is regarded as the label of the pharmaceutical product. The package insert incorporated into the article of manufacture indicates that Compound (I) is useful in the treatment of conditions wherein inhibition of PDE5 is desired. The package insert also provides instructions to administer one or more about 1 to about 20 mg unit dosage forms as needed, up to a maximum total dose of 20 mg per day. Preferably, the dose administered is about 5 to about 20 mg/day, more preferably about 5 to about 15 mg/day. Most preferably, a 10 mg dosage form is administered once per day.

Preferred conditions to be treated include sexual dysfunction (including male erectile dysfunction; and female sexual dysfunction, and more preferably female arousal disorder (FAD)). The preferred condition to be treated is male erectile dysfunction.

Significantly, the package insert supports the use of the product to treat sexual dysfunction in patients suffering from a retinal disease, for example, diabetic retinopathy or retinitis pigmentosa, or in patients who are using organic nitrates. Thus, the package insert preferably is free of contraindications associated with these conditions, and particularly the administration of the dosage form with an organic nitrate. More



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preferably, the package insert also is free of any cautions or warnings both associated with retinal diseases, particularly retinitis pigmentosa, and associated with individuals prone to vision abnormalities. Preferably, the package insert also reports incidences of flushing below 2%, preferably below 1%, and most preferably below 0.5%, of the patients administered the dosage form. The incidence rate of flushing demonstrates marked improvement over prior pharmaceutical products containing a PDE5 inhibitor.

The container used in the article of manufacture is conventional in the pharmaceutical arts. Generally, the container is a blister pack, foil packet, glass or plastic bottle and accompanying cap or closure, or other such article suitable for use by the patient or pharmacist. Preferably, the container is sized to accommodate 1-1000 solid dosage forms, preferably 1 to 500 solid dosage forms, and most preferably, 5 to 30 solid dosage forms.

Oral dosage forms are recognized by those skilled in the art to include, for example, such forms as liquid formulations, tablets, capsules, and gelcaps. Preferably the dosage forms are solid dosage forms, particularly, tablets comprising about 1 to about 20 mg of Compound (I). Any pharmaceutically acceptable excipients for oral use are suitable for preparation of such dosage forms. Suitable pharmaceutical dosage forms include coprecipitate forms described, for example, in Butler U.S. Patent No. 5,985,326, incorporated herein by reference. In preferred embodiments, the unit dosage form of the

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present invention is a solid free of a coprecipitate form of Compound (I), but rather contains solid Compound (I) as a free drug.

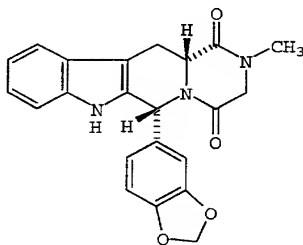
Preferably, the tablets comprise pharmaceutical excipients generally recognized as safe such as lactose, microcrystalline cellulose, starch, calcium carbonate, magnesium stearate, stearic acid, talc, and colloidal silicon dioxide, and are prepared by standard pharmaceutical manufacturing techniques as described in *Remington's Pharmaceutical Sciences, 18th Ed.*, Mack Publishing Co., Easton, PA (1990). Such techniques include, for example, wet granulation followed by drying, milling, and compression into tablets with or without film coating; dry granulation followed by milling, compression into tablets with or without film coating; dry blending followed by compression into tablets, with or without film coating; molded tablets; wet granulation, dried and filled into gelatin capsules; dry blend filled into gelatin capsules; or suspension and solution filled into gelatin capsules. Generally, the solid dosage forms have identifying marks which are debossed or imprinted on the surface.

The present invention is based on detailed experiments and clinical trials, and the unexpected observations that side effects previously believed to be indicative of PDE5 inhibition can be reduced to clinically insignificant levels by the selection of a compound and unit dose. This unexpected observation enabled the development of a unit dosage form that incorporates Compound (I) in about 1 to about 20 mg per unit dosage forms that, when orally administered, minimizes undesirable side effects previ-

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ously believed unavoidable. These side effects include facial flushing, vision abnormalities, and a significant decrease in blood pressure, when Compound (I) is administered alone or in combination with an organic nitrate. The minimal effect of Compound (I), administered in about 1 to about 20 mg unit dosage forms, on PDE6 also allows the administration of a selective PDE5 inhibitor to patients suffering from a retinal disease, like diabetic retinopathy or retinitis pigmentosa.

Compound (I) has the following structural formula:



(I)

The compound of structural formula (I) was demonstrated in human clinical studies to exert a minimal impact on systolic blood pressure when administered in conjunction with organic nitrates. By contrast, sildenafil demonstrates a four-fold greater decrease in systolic blood pressure over a placebo, which leads to the contraindications in the VIAGRA<sup>®</sup> insert, and in warnings to certain patients.

The following illustrates the PDE5 and PDE6 IC<sub>50</sub> values for the compound of structural

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formula (I) determined by the procedures described herein.

Compound	PDE5 IC <sub>50</sub> (nM)	PDE6 IC <sub>50</sub> (nM)	PDE6/PDE5
I	2.5	3400	1360

The compound of structural formula (I) additionally demonstrates an IC<sub>50</sub> against PDE1c of 10,000, and a ratio of PDE1c/PDE5 of 4,000.

### PREPARATIONS

#### Human PDE5 Preparation

Recombinant production of human PDE5 was carried out essentially as described in Example 7 of U.S. Patent No. 5,702,936, incorporated herein by reference, except that the yeast transformation vector employed, which is derived from the basic ADH2 plasmid described in V. Price et al., *Methods in Enzymology*, 1985, pages 308-318 (1990), incorporated yeast ADH2 promoter and terminator sequences rather than ADH1 promoter and terminator sequences and the *Saccharomyces cerevisiae* host was the protease-deficient strain BJ2-54 deposited on August 31, 1998 with the American Type Culture Collection, Manassas, Virginia, under accession number ATCC 74465. Transformed host cells were grown in 2X SC-leu medium, pH 6.2, with trace metals, and vitamins. After 24 hours, YEP medium containing glycerol was added to a final concentration of 2X YEP/3% glycerol. Approximately 24 hours later, cells were harvested, washed, and stored at -70°C.

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Cell pellets (29 g) were thawed on ice with an equal volume of lysis buffer (25 mM Tris-Cl, pH 8, 5 mM MgCl<sub>2</sub>, 0.25 mM dithiothreitol, 1 mM benzamidine, and 10  $\mu$ M ZnSO<sub>4</sub>). Cells were lysed in a microfluidizer with N<sub>2</sub> at 20,000 psi. The lysate was centrifuged and filtered through 0.45  $\mu$ m disposable filters. The filtrate was applied to a 150 mL column of Q Sepharose Fast Flow (Pharmacia). The column was washed with 1.5 volumes of Buffer A (20 mM Bis-Tris Propane, pH 6.8, 1 mM MgCl<sub>2</sub>, 0.25 mM dithiothreitol, 10  $\mu$ M ZnSO<sub>4</sub>) and eluted with a step gradient of 125 mM NaCl in Buffer A followed by a linear gradient of 125-1000 mM NaCl in Buffer A.

Active fractions from the linear gradient were applied to a 180 mL ceramic hydroxyapatite column in Buffer B (20 mM Bis-Tris Propane (pH 6.8), 1 mM MgCl<sub>2</sub>, 0.25 mM dithiothreitol, 10  $\mu$ M ZnSO<sub>4</sub>, and 250 mM KCl). After loading, the column was washed with 2 volumes of Buffer B and eluted with a linear gradient of 0-125 mM potassium phosphate in Buffer B. Active fractions were pooled, precipitated with 60% ammonium sulfate, and resuspended in Buffer C (20 mM Bis-Tris Propane, pH 6.8, 125 mM NaCl, 0.5 mM dithiothreitol, and 10  $\mu$ M ZnSO<sub>4</sub>). The pool was applied to a 140 mL column of Sephacryl S-300 HR and eluted with Buffer C. Active fractions were diluted to 50% glycerol and stored at -20°C. The resultant preparations were about 85% pure by SDS-PAGE.

#### Assay for PDE Activity

Activity of PDE5 can be measured by standard assays in the art. For example, specific

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activity of any PDE can be determined as follows.

PDE assays utilizing a charcoal separation technique were performed essentially as described in Loughney et al., (1996), *The Journal of Biological Chemistry*,

5 271:796-806. In this assay, PDE5 activity converts [ $^{32}$ P]cGMP to [ $^{32}$ P]5'GMP in proportion to the amount of PDE5 activity present. The [ $^{32}$ P]5'GMP then is

quantitatively converted to free [ $^{32}$ P] phosphate and unlabeled adenosine by the action of snake venom 5'-nucleotidase. Hence, the amount of [ $^{32}$ P] phosphate

10 liberated is proportional to enzyme activity. The assay is performed at 30 C in a 100  $\mu$ L reaction mixture containing (final concentrations) 40 mM Tris-Cl (pH 8.0), 1  $\mu$ M ZnSO<sub>4</sub>, 5 mM MgCl<sub>2</sub>, and 0.1

15 mg/mL bovine serum albumin. PDE5 is present in quantities that yield <30% total hydrolysis of substrate (linear assay conditions). The assay is initiated by addition of substrate (1 mM [ $^{32}$ P]cGMP), and the mixture is incubated for 12 minutes.

20 Seventy-five (75)  $\mu$ g of *Crotalus atrox* venom then is added, and the incubation is continued for 3 more minutes (15 minutes total). The reaction is stopped by addition of 200 mL of activated charcoal (25 mg/-mL suspension in 0.1 M NaH<sub>2</sub>PO<sub>4</sub>, pH 4). After

25 centrifugation (750 x g for 3 minutes) to sediment the charcoal, a sample of the supernatant is taken for radioactivity determination in a scintillation counter and the PDE5 activity is calculated. The preparations had specific activities of about 3

30  $\mu$ moles cGMP hydrolyzed per minute per milligram protein.

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Bovine PDE6 Preparation

Bovine PDE6 was supplied by Dr. N. Virmaux, INSERM U338, Strasbourg. Bovine retinas were prepared as described by Virmaux et al., *FEBS Letters*, 12(6), pp. 325-328 (1971) and see also, A. Sitaramayya et al., *Exp. Eye Res.*, 25, pp. 163-169 (1977). Briefly, unless stated otherwise, all operations were done in the cold and in dim red light. Eyes were kept in the cold and in the dark for up to four hours after slaughtering.

Preparation of bovine retinal outer segment (ROS) basically followed procedures described by Schichi et al., *J. Biol. Chem.*, 224:529 (1969). In a typical experiment, 35 bovine retinas were ground in a mortar with 35 mL 0.066 M phosphate buffer, pH 7.0, made up to 40% with sucrose, followed by homogenization in a Potter homogenizer (20 up and down strokes). The suspension was centrifuged at 25,000 x g for 20 minutes. The pellet was homogenized in 7.5 mL 0.006 M phosphate buffer (40% in sucrose), and carefully layered under 7.5 mL of phosphate buffer (containing no sucrose). Centrifugation was conducted in a swing-out rotor at 45,000 x g for 20 minutes, and produced a pellet which is black at the bottom, and also a red band at the interface 0.066 M. phosphate--40% sucrose/0.066 M phosphate (crude ROS). The red material at the interface was removed, diluted with phosphate buffer, spun down to a pellet, and redistributed in buffered 40% sucrose as described above. This procedure was repeated 2 or 3 times until no pellet was formed. The purified ROS was washed in phosphate

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buffer and finally spun down to a pellet at 25,000 x g for 20 minutes. All materials were then kept frozen until used.

5 Hypotonic extracts were prepared by suspending isolated ROS in 10 mM Tris-Cl pH 7.5, 1 mM EDTA, and 1 mM dithioerythritol, followed by centrifugation at 100,000 x g for 30 minutes.

10 The preparation was reported to have a specific activity of about 35 nmoles cGMP hydrolyzed per minute per milligram protein.

**PDE1c Preparation from *Spodoptera fugiperda* Cells (Sf9)**

15 Cell pellets (5g) were thawed on ice with 20ml of Lysis Buffer (50mM MOPS pH 7.4, 10 $\mu$ M ZnSO<sub>4</sub>, 0.1mM CaCl<sub>2</sub>, 1mM DTT, 2mM benzamidine HCl, 5 $\mu$ g/ml each of pepstatin, leupeptin, and aprotinin). Cells  
20 were lysed by passage through a French pressure cell (SLM-Aminco) while temperatures were maintained below 10°C. The resultant cell homogenate was centrifuged at 36,000 rpm at 4°C for 45 minutes in a Beckman ultracentrifuge using a Type TI45 rotor.  
25 The supernatant was discarded and the resultant pellet was resuspended with 40 ml of Solubilization Buffer (Lysis Buffer containing 1M NaCl, 0.1M MgCl<sub>2</sub>, 1mM CaCl<sub>2</sub>, 20 $\mu$ g/ml calmodulin, and 1% Sulfo betaine SB12 (Z3-12) by sonicating using a VibraCell tuner  
30 with a microtip for 3 x 30 seconds. This was performed in a crushed ice/salt mix for cooling. Following sonication, the mixture was slowly mixed for 30 minutes at 4°C to finish solubilizing membrane bound proteins. This mixture was centrifuged



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in a Beckman ultracentrifuge using a type TI45 rotor at 36,000 rpm for 45 minutes. The supernatant was diluted with Lysis Buffer containing 10µg/ml calpain inhibitor I and II. The precipitated protein was  
5 centrifuged for 20 minutes at 9,000 rpm in a Beckman JA-10 rotor. The recovered supernatant then was subjected to Mimetic Blue AP Agarose Chromatography.

In order to run the Mimetic Blue AP Agarose Column, the resin initially was shielded by  
10 the application of 10 bed volumes of 1% polyvinylpyrrolidone (i.e., MW of 40,000) to block nonspecific binding sites. The loosely bound PVP-40 was removed by washing with 10 bed volumes of 2M NaCl, and 10 mM sodium citrate pH 3.4. Just prior to  
15 addition of the solubilized PDE1c3 sample, the column was equilibrated with 5 bed volumes of Column Buffer A (50 mM MOPS pH 7.4, 10µM ZnSO<sub>4</sub>, 5mM MgCl<sub>2</sub>, 0.1 mM CaCl<sub>2</sub>, 1 mM DTT, 2 mM benzamidine HCl).

The solubilized sample was applied to the  
20 column at a flow rate of 2 ml/min with recycling such that the total sample was applied 4 to 5 times in 12 hours. After loading was completed, the column was washed with 10 column volumes of Column Buffer A, followed by 5 column volumes of Column  
25 Buffer B (Column Buffer A containing 20 mM 5'-AMP), and followed by 5 column volumes of Column Buffer C (50 mM MOPS pH 7.4, 10 µM ZnSO<sub>4</sub>, 0.1 mM CaCl<sub>2</sub>, 1 mM dithiothreitol, and 2 mM benzamidine HCl). The enzyme was eluted into three successive pools. The  
30 first pool consisted of enzyme from a 5 bed volume wash with Column Buffer C containing 1 mM cAMP. The second pool consisted of enzyme from a 10 bed volume wash with Column Buffer C containing 1 M NaCl. The

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final pool of enzyme consisted of a 5 bed volume wash with Column Buffer C containing 1 M NaCl and 20 mM cAMP.

The active pools of enzyme were collected and the cyclic nucleotide removed via conventional gel filtration chromatography or chromatography on hydroxy-apatite resins. Following removal of cyclic nucleotides, the enzyme pools were dialyzed against Dialysis Buffer containing 25 mM MOPS pH 7.4, 10  $\mu$ M ZnSO<sub>4</sub>, 500 mM NaCl, 1 mM CaCl<sub>2</sub>, 1 mM dithiothreitol, 1 mM benzamidinium HCl, followed by dialysis against Dialysis buffer containing 50% glycerol. The enzyme was quick frozen with the aid of dry ice and stored at -70°C.

The resultant preparations were about >90% pure by SDS-PAGE. These preparations had specific activities of about 0.1 to 1.0  $\mu$ mol cAMP hydrolyzed per minute per milligram protein.

#### IC<sub>50</sub> Determinations

The parameter of interest in evaluating the potency of a competitive enzyme inhibitor of PDE5 and/or PDE1c and PDE6 is the inhibition constant, i.e., K<sub>i</sub>. This parameter can be approximated by determining the IC<sub>50</sub>, which is the inhibitor concentration that results in 50% enzyme inhibition, in a single dose-response experiment under the following conditions.

The concentration of inhibitor is always much greater than the concentration of enzyme, so that free inhibitor concentration (which is unknown)

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is approximated by total inhibitor concentration (which is known).

A suitable range of inhibitor concentrations is chosen (i.e., inhibitor concentrations at least several fold greater and several fold less than the  $K_i$  are present in the experiment). Typically, inhibitor concentrations ranged from 10 nM to 10  $\mu$ M.

The concentrations of enzyme and substrate are chosen such that less than 20% of the substrate is consumed in the absence of inhibitor (providing, e.g., maximum substrate hydrolysis of from 10 to 15%), so that enzyme activity is approximately constant throughout the assay.

The concentration of substrate is less than one-tenth the Michaelis constant ( $K_m$ ). Under these conditions, the  $IC_{50}$  will closely approximate the  $K_i$ . This is because of the Cheng-Prusoff equation relating these two parameters:  $IC_{50}=K_i(1+S/K_m)$ , with  $(1+S/K_m)$  approximately 1 at low values of  $S/K_m$ .

The  $IC_{50}$  value is estimated from the data points by fitting the data to a suitable model of the enzyme inhibitor interaction. When this interaction is known to involve simple competition of the inhibitor with the substrate, a two-parameter model can be used:

$$Y=A/(1+x/B)$$

where the  $y$  is the enzyme activity measured at an inhibitor concentration of  $x$ ,  $A$  is the activity in the absence of inhibitor and  $B$  is the  $IC_{50}$ . See Y.

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Cheng et al., *Biochem. Pharmacol.*, 22:3099-3108 (1973).

Effects of inhibitors of the present invention on enzymatic activity of PDE5 and PDE6 preparations as described above were assessed in either of two assays which differed from each other principally on the basis of scale and provided essentially the same results in terms of  $IC_{50}$  values. Both assays involved modification of the procedure of Wells et al., *Biochim. Biophys. Acta*, 384:430 (1975). The first of the assays was performed in a total volume of 200  $\mu$ l containing 50 mM Tris pH 7.5, 3 mM Mg acetate, 1 mM EDTA, 50  $\mu$ g/mL snake venom nucleotidase and 50 nM [ $^3$ H]-cGMP (Amersham). Compounds of the invention were dissolved in DMSO finally present at 2% in the assay. The assays were incubated for 30 minutes at 30°C and stopped by addition of 800  $\mu$ l of 10 mM Tris pH 7.5, 10 mM EDTA, 10 mM theophylline, 0.1 mM adenosine, and 0.1 mM guanosine. The mixtures were loaded on to 0.5 mL QAE Sephadex columns, and eluted with 2 mL of 0.1 M formate (pH 7.4). The eluted radioactivity was measured by scintillation counting in Optiphase Hisafe 3.

A second, microplate, PDE assay was developed using Multiscreen plates and a vacuum manifold. The assay (100  $\mu$ l) contained 50 mM Tris pH 7.5, 5 mM Mg acetate, 1 mM EDTA and 250  $\mu$ g/mL snake venom nucleotidase. The other components of the reaction mixture were as described above. At the end of the incubation, the total volume of the assays were loaded on a QAE Sephadex microcolumn plate by filtration. Free radioactivity was eluted

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with 200  $\mu$ l of water from which 50  $\mu$ l aliquots were analyzed by scintillation counting as described above.

The following examples are presented to further illustrate the preparation of the claimed invention. The scope of the present invention is not to be construed as merely consisting of the following examples.

#### Example 1

Compound (I) was prepared as described in U.S. patent 5,859,006 and formulated in tablets using wet granulation. Povidone was dissolved in water to make a 10% solution. The active compound, microcrystalline cellulose, croscarmellose sodium, and sodium lauryl sulfate were added to a high shear mixer and mixed for 2 minutes. The powders were wet granulated with the povidone solution and extra water as required to complete the granulation. The resultant mixture was dried in a fluid bed drier with inlet air at  $70^{\circ}\text{C} \pm 5^{\circ}\text{C}$  until the loss on drying was below 2.5%. The granules were passed through a Comil with a suitable screen (or a sieve) and added to a suitable mixer. The extragranular croscarmellose sodium and sodium lauryl sulfate, and the colloidal anhydrous silica were passed through a suitable sieve (e.g., 500 micron) and added to the mixer and blended 5 minutes. Magnesium stearate was added and blended for 2 minutes. The blend was compressed to a target compression/weight of 250 mg using 9 mm round normal concave tooling.

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The core tablets were coated with an aqueous suspension of Opadry OY-S-7322 using an Accelacota (or similar coating pan) using inlet air at 50°C to 70°C until the tablet weight was increased by approximately 8 mg. Opadry OY-S-7322 contains methylhydroxypropylcellulose Ph.Eur., titanium dioxide Ph. Eur., Triacetin USP. Opadry increases the weight of each tablet to about 258 mg. The amount of film coat applied per tablet may be less than that stated depending on the process efficiency.

The tablets are filled into blister packs and accompanied by package insert describing the safety and efficacy of the compound.

Component	Formulations (mg per tablet)	
Selective PDE5 Inhibitor <sup>1)</sup>	1	5
Hydroxypropyl Methylcellulose Phthalate	1	5
Microcrystalline Cellulose	221.87	213.87
Croscarmellose Sodium	5.00	5.00
Sodium Lauryl Sulfate	2.50	2.50
Povidone K30	9.38	9.38
Purified Water, USP (water for irrigation)	q.s.	q.s.
Croscarmellose Sodium	5.00	5.00
Sodium Lauryl Sulfate	2.50	2.50
Colloidal Anhydrous Silica	0.50	0.50
Magnesium Stearate	1.25	1.25
Total core subtotal	250.00	250.00
(Film coat Opadry OY-S-7322)	about 8 mg	about 8 mg

<sup>1)</sup> Compound (I).

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Example 2

The following formula is used in preparing the finished dosage form containing 10 mg of Compound (I).

Ingredient	Quantity (mg)
<u>Granulation</u>	
Selective PDE5 Inhibitor <sup>1)</sup>	10.00
Lactose Monohydrate	153.80
Lactose Monohydrate (spray dried)	25.00
Hydroxypropylcellulose	4.00
Croscarmellose Sodium	9.00
Hydroxypropylcellulose (EF)	1.75
Sodium Lauryl Sulfate	0.70
	35.00
<u>Outside Powders</u>	
Microcrystalline Cellulose (granular-102)	37.50
Croscarmellose Sodium	7.00
Magnesium Stearate (vegetable)	1.25
	<b>Total 250 mg</b>
Film coat (approximately) 11.25	

Purified Water, USP is used in the manufacture of the tablets. The water is removed during processing and minimal levels remain in the finished product.

Tablets are manufactured using a wet granulation process. A step-by-step description of the process is as follows. The drug and excipients to be granulated are security sieved. The selective

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PDE5 inhibitor is dry blended with lactose monohydrate (spray dried), hydroxypropylcellulose, croscarmellose sodium, and lactose monohydrate. The resulting powder blend is granulated with an aqueous solution of hydroxypropylcellulose and sodium lauryl sulfate using a Powrex or other suitable high shear granulator. Additional water can be added to reach the desired endpoint. A mill can be used to delump the wet granulation and facilitate drying. The wet granulation is dried using either a fluid bed dryer or a drying oven. Once the material is dried, it can be sized to eliminate any large agglomerates. Microcrystalline cellulose, croscarmellose sodium, and magnesium stearate are security sieved and added to the dry sized granules. These excipients and the dry granulation are mixed until uniform using a tumble bin, ribbon mixer, or other suitable mixing equipment. The mixing process can be separated into two phases. The microcrystalline cellulose, croscarmellose sodium, and the dried granulation are added to the mixer and blended during the first phase, followed by the addition of the magnesium stearate to this granulation and a second mixing phase.

The mixed granulation then is compressed into tablets using a rotary compression machine. The core tablets are film coated with an aqueous suspension of the appropriate color mixture in a coating pan (e.g., Accela Cota). The coated tablets can be lightly dusted with talc to improve tablet handling characteristics.

The tablets are filled into plastic containers (30 tablets/container) and accompanied by



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package insert describing the safety and efficacy of the compound.

Example 3

The following formula is used in preparing a finished dosage form containing 5 mg of Compound (I).

Ingredient	Quantity (mg)
<u>Granulation</u>	
Selective PDE5 Inhibitor <sup>1)</sup>	2.50
Lactose Monohydrate	79.395
Lactose Monohydrate (spray dried)	12.50
Hydroxypropylcellulose	2.00
Croscarmellose Sodium	4.50
Hydroxypropylcellulose (EF)	0.875
Sodium Lauryl Sulfate	0.35
<u>Outside Powders</u>	
Microcrystalline Cellulose (granular-102)	18.75
Croscarmellose Sodium	3.50
Magnesium Stearate (vegetable)	0.63
	<b>Total 125 mg</b>
Film coat (approximately) 6.875	

The dosage form of Example 3 was prepared in an identical manner to the dosage form of Example 2.

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Example 4

Solution Capsule		
Ingredient	mg/capsule	Percent (%)
Selective PDE5 Inhibitor <sup>1)</sup>	10	2
PEG400 NF	490	98
Fill Weight	500	100

The gelatin capsules are precisely filled by pumping an accurate fill volume of pre-dissolved drug formulation into the partially sealed cavity of a capsule. Immediately following injection fill of the drug solution formulation, the capsule is completely heat sealed.

The capsules are filled into plastic containers and accompanied by a package insert.

Example 5

This study was a randomized, double-blind, placebo-controlled, two-way crossover design clinical pharmacology drug interaction study that evaluated the hemodynamic effects of concomitant administration of a selective PDE5 inhibitor (i.e., Compound (I)) and short-acting nitrates on healthy male volunteers. In this study, the subjects received either Compound (I) at a dose of 10 mg or a placebo, daily for seven days. On the sixth or seventh day, the subjects received sublingual nitroglycerin (0.4 mg) while supine on a tilt table. The nitroglycerin was administered 3 hours after Compound (I) dosing, and all subjects kept the nitroglycerine tablet

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under their tongue until it completely dissolved. The subjects were tilted to 70° head-up every 5 minutes for a total of 30 minutes with measurement of blood pressure and heart rate. There were no  
5 discontinuations among the twenty-two healthy male subjects (ages 19 to 60 years old) that entered this study.

In a preliminary analysis of this study, Compound (I) was well tolerated and there were no  
10 serious adverse events. There were no Compound (I) changes in laboratory safety assessments or 12-lead ECGs. The most common adverse events were headache, dyspepsia, and back pain. Compound (I) demonstrated minimal, if any, effect on mean systolic blood  
15 pressure, and mean maximal nitroglycerin-induced decrease in systolic blood pressure.

#### Example 6

20 In two randomized, double-blinded placebo controlled studies, Compound (I) was administered to patients in need thereof at a range of doses, in both daily dosing and for on demand therapy, for  
25 sexual encounters and intercourse in the home setting. Doses from 5 to 20 mg of Compound (I) were efficacious and demonstrated less than 1% flushing and no reports of vision abnormalities. It was  
30 found that a 10 mg dose of Compound (I) was fully efficacious and demonstrated minimal side effects.

Enhanced erectile function was determined by the International Index of Erectile Function (IIEF) (Rosen et al., *Urology*, 49, pp. 822-830

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(1997)), diaries of sexual attempts, and a global satisfaction question. Compound (I) significantly improved the percentage of successful intercourse attempts including the ability to attain and  
5 maintain an erection in both "on demand" and daily dosing regimens.

#### Example 7

10 A third clinical study was a randomized, double-blind, placebo-controlled study of Compound (I) administered "on demand" to patients with male erectile dysfunction. Compound (I) was administered over a period of eight weeks in the treatment of  
15 male erectile dysfunction (ED). Erectile dysfunction (ED) is defined as the persistent inability to attain and/or maintain an erection adequate to permit satisfactory sexual performance. "On demand" dosing is defined as intermittent administration of  
20 Compound (I) prior to expected sexual activity.

The study population consisted of 212 men, at least 18 years of age, with mild to severe erectile dysfunction. Compound (I) was orally administered as tablets of coprecipitate made in  
25 accordance with Butler U.S. Patent No. 5,985,326. Compound (I) was administered in 2 mg, 5 mg, 10 mg, and 25 mg doses, "on demand" and not more than once every 24 hours. Treatment with all nitrates, azole antifungals (e.g., ketoconazole or itraconazole),  
30 warfarin, erythromycin, or antiandrogens was not allowed at any time during the study. No other approved or experimental medications, treatments, or

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devices used to treat ED were allowed. Forty-one subjects were administered a placebo.

5       The two primary efficacy variables were the ability of a subject to penetrate his partner and his ability to maintain an erection during intercourse, as measured by the International Index of Erectile Function (IIEF). The IIEF Questionnaire contains fifteen questions, and is a brief, reliable measure of erectile function. See R.C. Rosen et al., *Urology*, 49, pp. 822-830 (1997).

10       Secondary efficacy variables were IIEF domain scores for erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction; the patient's ability to achieve an erection, ability to insert his penis into his partner's vagina, completion of intercourse with ejaculation, satisfaction with the hardness of his erection, and overall satisfaction, all as measured by the Sexual Encounter Profile (SEP) diary; and a global assessment question asked at the end of the treatment period. The SEP is a patient diary instrument documenting each sexual encounter during the course of the study.

25       The safety aspect of the study included all enrolled subjects, and was assessed by evaluating all reported adverse events, and changes in clinical laboratory values, vital signs, physical examination results, and electrocardiogram results.

30       At endpoint, patients who rated their penetration ability (IIEF Question 3) as "almost always or always" were as follows: 17.5% in the placebo group, 38.1% in the 2 mg group, 48.8% in the 5 mg group, 51.2% in the 10 mg group, and 83.7% in

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the 25 mg group. Comparisons revealed statistically significant differences in change in penetration ability between placebo and all dose levels of Compound (I).

5           At endpoint, patients who rated their ability to maintain an erection (IIEF Question 4) during intercourse as "almost always or always" are as follows: 10.0% in the placebo group, 19.5% in the 2 mg group, 32.6% in the 5 mg group, 39.0% in the 10 mg group, and 69.0% in the 25 mg group. Comparison revealed statistically significant differences in change in penetration ability between placebo and the three higher dose levels of Compound (I).

15           This study also included a safety evaluation. A treatment-emergent adverse event is defined as a condition not present at baseline that appeared postbaseline, or a condition present at baseline that increased in severity postbaseline. 20           The most commonly reported treatment-emergent adverse events were headache, dyspepsia, and back pain. The incidence of treatment-emergent adverse events appeared related to dose.

25           Overall, this study demonstrated that all four doses of Compound (I), namely 2 mg, 5 mg, 10 mg, and 25 mg, taken "on demand" produced significant improvement, relative to placebo, in the sexual performance of men with erectile dysfunction as assessed by the IIEF, by patient diaries assessing 30           frequency of successful intercourse and intercourse satisfaction, and by a global assessment.

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The combined results from clinical studies showed that administration of Compound (I) effectively treats male erectile dysfunction, as illustrated in the following table.

5

10

15

IIEF ERECTILE FUNCTION DOMAIN (Change from Baseline)			
Unit Dose of Compound (I)	n	Mean $\pm$ SD	p
placebo	131	0.8 $\pm$ 5.3	
2 mg	75	3.9 $\pm$ 6.1	<.001
5 mg	79	6.6 $\pm$ 7.1	<.001
10 mg	135	7.9 $\pm$ 6.7	<.001
25 mg	132	9.4 $\pm$ 7.0	<.001
50 mg	52	9.8 $\pm$ 5.5	<.001
100 mg	49	8.4 $\pm$ 6.1	<.001

n is number of subjects, SD is standard deviation.

20

25

However, it also was observed from the combined clinical studies that the percent of treatment-emergent adverse events increased with an increasing unit dose of Compound (I), as illustrated in the following table:

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Treatment-Emergent Adverse Events (%)							
Unit Dose of Compound (I) (mg)							
Event	Placebo	2	5	10	25	50	100
Headache	10	12	10	23	29	34	46
Dyspepsia	6	3	14	13	19	20	25
Back Pain	5	3	3	15	18	24	22
Myalgia	3	0	3	9	16	20	29
Rhinitis	3	7	3	4	4	0	2
Conjunctivitis	1	0	1	1	0	2	5
Eyelid Edema	0	0	0	1	1	2	3
Flushing	0	0	0	<1	0	3	7
Vision Abnormalities	0	0	0	0	0	0	0

The above table shows an increase in adverse events at 25 mg through 100 mg unit doses. Accordingly, even though efficacy in the treatment of ED was observed at 25 mg to 100 mg doses, the adverse events observed from 25 mg to 100 mg doses must be considered.

In accordance with the present invention, a unit dose of about 1 to about 20 mg, preferably about 2 to about 20 mg, more preferably about 5 to about 20 mg, and most preferably about 5 to about 15 mg, of Compound (I), administered up to a maximum of 20 mg per 24-hour period, both effectively treats ED and minimizes or eliminates the occurrence of adverse side effects. Importantly, no vision abnormalities were reported and flushing was essentially eliminated. Surprisingly, in addition to treating ED, with at about 1 to about 20 mg unit dose Compound (I), with a minimum of adverse side effects, individuals undergoing nitrate therapy also can be



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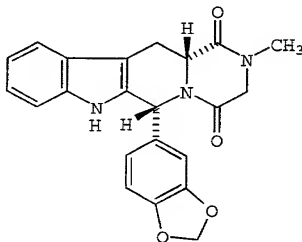
treated for ED by the method and composition of the present invention.

The principles, preferred embodiments, and modes of operation of the present invention have  
5 been described in the foregoing specification. The invention intended to be protected herein, however, is not construed to be limited to the particular forms disclosed, because they are to be regarded as illustrative rather than restrictive. Variations  
10 and changes may be made by those skilled in the art without departing from the spirit of the invention.

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## WHAT IS CLAIMED IS:

1. A pharmaceutical unit dosage composition comprising about 1 to about 20 mg of a compound having the structural formula:



said unit dosage form suitable for oral administration.

2. The dosage form of claim 1 comprising about 2 to about 20 mg of the compound in unit dosage form.

3. The dosage form of claim 1 comprising about 5 to about 20 mg of the compound in unit dosage form.

4. The dosage form of claim 2 comprising about 2.5 mg of the compound in unit dosage form.

5. The dosage form of claim 3 comprising about 5 mg of the compound in unit dosage form.

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6. The dosage form of claim 3 comprising about 10 mg of the compound in unit dosage form.

7. The dosage form of claims 1 through 6 wherein the unit dose is in a form selected from the group consisting of a liquid, a tablet, a capsule, and a gelcap.

8. The dosage form of claims 1 through 6 wherein the unit dose is in the form of a tablet.

9. The dosage form of claims 1 through 6 for use in treating a condition where inhibition of PDE5 is desirable.

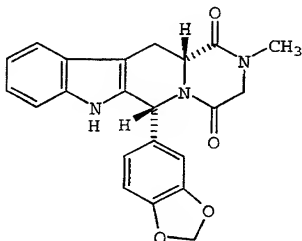
10. The dosage form of claim 9 wherein the condition is a sexual dysfunction.

11. The dosage form of claim 10 wherein the sexual dysfunction is male erectile dysfunction.

12. The dosage form of claim 10 wherein the sexual dysfunction is female arousal disorder.

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13. A method of treating sexual dysfunction in a patient in need thereof comprising administering one or more unit dose containing about 1 to about 20 mg, up to a maximum total dose of 20 mg per day, of a compound having the structure



14. The method of claim 13 wherein the unit dose contains about 2 to about 20 mg of the compound.

15. The method of claim 13 wherein the unit dose contains about 5 mg of the compound.

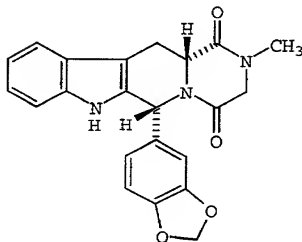
16. The method of claim 13 wherein the unit dose contains about 10 mg of the compound and is administered once per day.

17. The method of claim 13 wherein the unit dose is in a form selected from the group consisting of a liquid, a tablet, a capsule, and a gelcap.

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18. The invention as hereinbefore described.

19. Use of a unit dose containing about 1 to about 20 mg of a compound having the structure



for the manufacture of a medicament for the treatment of sexual dysfunction in a patient in need thereof.

## DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name; I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled "UNIT DOSAGE FORM," the specification of which (check one): ☐ is attached hereto; ☐ was filed on \_\_\_\_\_ as Application Serial No. \_\_\_\_\_ and was amended on \_\_\_\_\_ (if applicable); ☒ was filed as PCT International Application No. PCT/US00/11129 on April 26, 2000, and was amended under Article 19 on \_\_\_\_\_ (if applicable). I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above. I acknowledge the duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in 37 C.F.R. §1.56.

I hereby claim foreign priority benefits under 35 U.S.C. §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PCT/US00/11129	PCT	26/04/00	Priority Claimed	
(Application Serial Number)	(Country)	(Day/Month/Year Filed)	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
_____	_____	_____	<input type="checkbox"/> Yes	<input type="checkbox"/> No
_____	_____	_____	<input type="checkbox"/> Yes	<input type="checkbox"/> No

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below:

60/132,036	30/04/99
(Application Serial Number)	(Day/Month/Year Filed)
_____	_____
_____	_____

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s) or PCT international application(s) designating the United States of America listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior application(s) in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in 37 C.F.R. §1.56 which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

(Application Serial Number)	(Day/Month/Year Filed)	(Status-Patented, Pending or Abandoned)
_____	_____	_____
_____	_____	_____

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: I hereby appoint as my attorneys, with full powers of substitution and revocation, to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

John B. Lungmus (18,566)  
Allen H. Gerstein (22,218)  
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David A. Gass (38,153)  
Gregory C. Mayer (38,238)  
Michael R. Weiner (38,359)  
William K. Merkel (40,725)

Send correspondence to: James J. Napoli

FIRM NAME	PHONE NO.	STREET	CITY & STATE	ZIP CODE
Marshall, Gerstein & Borun	312-474-6300	<u>6300 Sears Tower</u> <u>233 South Wacker Drive</u>	<u>Chicago, Illinois</u>	<u>60606-6402</u>

Full Name of First or Sole Inventor <u>William Ernest Pullman</u>	Citizenship <u>United States of America</u> <u>AUSTRALIA</u>
Residence Address - Street <u>42 Annin Road</u>	Post Office Address - Street <u>42 Annin Road</u>
City (Zip) <u>Far Hills (07931)</u>	City (Zip) <u>Far Hills (07931)</u>
State or Country <u>New Jersey</u>	State or Country <u>New Jersey</u>
Date <u>11/10/01</u>	Signature <u>[Signature]</u>

Second Joint Inventor, if any <u>John Steven Whitaker</u>	Citizenship <u>United States of America</u>
Residence Address - Street <u>19340 162nd Avenue</u>	Post Office Address - Street <u>19342 162nd Avenue</u>
City (Zip) <u>Woodinville (98072)</u>	City (Zip) <u>Woodinville (98072)</u>
State or Country <u>Washington</u>	State or Country <u>Washington</u>
Date <u>[Blank]</u>	Signature <u>[Blank]</u>

Third Joint Inventor, if any	Citizenship
Residence Address - Street	Post Office Address - Street
City (Zip)	City (Zip)
State or Country	State or Country
Date <u>[Blank]</u>	Signature <u>[Blank]</u>

Fourth Joint Inventor, if any	Citizenship
Residence Address - Street	Post Office Address - Street
City (Zip)	City (Zip)
State or Country	State or Country
Date <u>[Blank]</u>	Signature <u>[Blank]</u>

## APPLICABLE RULES AND STATUTES

### 37 CFR 1.56. DUTY OF DISCLOSURE - INFORMATION MATERIAL TO PATENTABILITY (Applicable Portion)

(a) A patent by its very nature is affected with a public interest. The public interest is best served, and the most effective patent examination occurs when, at the time an application is being examined, the Office is aware of and evaluates the teachings of all information material to patentability. Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section. The duty to disclose information exists with respect to each pending claim until the claim is canceled or withdrawn from consideration, or the application becomes abandoned. Information material to the patentability of a claim that is canceled or withdrawn from consideration need not be submitted if the information is not material to the patentability of any claim remaining under consideration in the application. There is no duty to submit information which is not material to the patentability of any existing claim. The duty to disclose all information known to be material to patentability is deemed to be satisfied if all information known to be material to patentability of any claim issued in a patent was cited by the Office or submitted to the Office in the manner prescribed by §§ 1.97(b)-(d) and 1.98. However, no patent will be granted on an application in connection with which fraud on the Office was practiced or attempted or the duty of disclosure was violated through bad faith or intentional misconduct. The Office encourages applicants to carefully examine:

- (1) prior art cited in search reports of a foreign patent office in a counterpart application, and
- (2) the closest information over which individuals associated with the filing or prosecution of a patent application believe any pending claim patentability defines, to make sure that any material information contained therein is disclosed to the Office.

Information relating to the following factual situations enumerated in 35 USC 102 and 103 may be considered material under 37 CFR 1.56(a).

### 35 U.S.C. 102. CONDITIONS FOR PATENTABILITY: NOVELTY AND LOSS OF RIGHT TO PATENT

A person shall be entitled to a patent unless --

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States, or
- (c) he has abandoned the invention, or
- (d) the invention was first patented or caused to be patented, or was the subject of an inventor's certificate, by the applicant or his legal representatives or assigns in a foreign country prior to the date of the application for patent in this country on an application for patent or inventor's certificate filed more than twelve months before the filing of the application in the United States, or
- (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraph (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent, or
- (f) he did not himself invent the subject matter sought to be patented, or
- (g) before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

### 35 U.S.C. 103. CONDITIONS FOR PATENTABILITY; NON-OBVIOUS SUBJECT MATTER (Applicable Portion)

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

### 35 U.S.C. 112. SPECIFICATION (Applicable Portion)

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.



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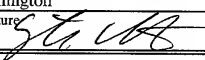
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Full Name of First or Sole Inventor <b>William Ernest Pullman</b>	Citizenship <b>United States of America</b>
Residence Address - Street <b>3004 Towne Drive</b>	Post Office Address - Street <b>3004 Towne Drive</b>
City (Zip) <b>Carmel (46032)</b>	City (Zip) <b>Carmel (46032)</b>
State or Country <b>Indiana</b>	State or Country <b>Indiana</b>
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Date <b>11 Oct 2001</b> <input checked="" type="checkbox"/>	Signature  <input checked="" type="checkbox"/>

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- (c) he has abandoned the invention, or
- (d) the invention was first patented or caused to be patented, or was the subject of an inventor's certificate, by the applicant or his legal representatives or assigns in a foreign country prior to the date of the application for patent in this country on an application for patent or inventor's certificate filed more than twelve months before the filing of the application in the United States, or
- (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraph (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent, or
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